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AMINOALKYL-BENZOFURAN-5-OL COMPOUNDS FOR THE TREATMENT OF GLAUCOMA

BACKGROUND OF THE INVENTION

1. Field of the Invention

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The present invention relates to treatment for lowering intraocular pressure and to compounds for use in such treatments. More particularly, the present invention relates to the use of compounds with serotonergic 5-HT5-HT₂ agonist activity to lower intraocular pressure (IOP), treat glaucoma, and to provide neuroprotection.

2. Description of the Related Art

Serotonin (5-hydroxy tryptamine; 5-HT5-HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion 1992; Hoyer et al. 1994; Tobin et al. 1988].

5-HT is known to interact with at least seven major 5-HT receptors (5-HT₁-5-HT₇) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer et al. 1994; Martin et al. 1998]. Receptor subtypes within the 5-HT₁ family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5-HT₄, 5-HT₆, and 5-HT₇ receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5-HT [Martin et al. 1998]. The receptors in the 5-HT₂ family are positively coupled to phospholipase C (PLC) and thus

generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5-HT. The 5-HT₃ receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer et al. 1994].

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The human and animal 5-HT, receptor has only recently been cloned, expressed, and shown to be present in various brain areas and peripheral tissues [Eglen et al. 1997]. Recent studies have shown there to be four splice variants of the 5-HT, receptor [Heidmann et al. 1997]. It has been proposed that the 5-HT, receptor may be involved in the pathophysiology of sleep disorders, depression, and other psychiatric disorders [Eglen et al. 1997]. In the periphery, stimulation of 5-HT, receptors results in relaxation of blood vessels and hence vasodilation [Eglen et al. 1997].

Known compounds exhibiting 5-HT₂ agonist activity have typically been designed to treat numerous central nervous system (CNS)-related conditions, particularly the treatment of obesity and depression, by activation of 5-HT_{2C} receptors. Thus, one desired property of known 5-HT₂ agonist compounds is that they easily penetrate the blood brain barrier. Compounds possessing the property of penetration into the CNS generally do not contain polar groups.

To treat ocular diseases, it is desirable to administer compositions orally or topically that will remain in the ocular tissues and not cross the blood brain barrier to enter the CNS. What are needed are 5-HT₂ agonist compounds that are useful in the treatment of ocular diseases characterized by an elevated intraocular pressure, the treatment of glaucoma and neuroprotection. Such compounds would not have a propensity to cross the blood brain barrier.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing compounds having 5-HT₂ agonist activity that do not cross the blood brain barrier. More specifically, the present invention provides compounds having the following general formula:

wherein R¹ is hydrogen or C₁₋₄alkyl; R² is hydrogen, C₁₋₄alkyl, or R¹ and R² can together be (CH₂)₂₋₄ to complete a heterocyclic ring; R³ is hydrogen, hydroxyl, C₁₋₄alkoxy, or fluorine; R⁴ is selected from C₁₋₄alkyl, halogen, nitrile, C₁₋₆alkylthiol, trifluoromethyl, C₁₋₄alkyl substituted by HO or C₁₋₃alkoxy, R⁵ is hydrogen, halogen, C₁₋₄alkoxy, nitrile, W is hydrogen or C(=O)C₁₋₈alkyl. In preferred embodiments, R¹, R³ and R⁵ are hydrogen, R² is methyl, R⁴ is halogen, methyl or trifluoromethyl, and W is hydrogen. Most preferably, the compounds of the invention have an R-configuration at the carbon atom bearing the primary amine.

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In another aspect, the present invention provides compositions containing the compounds described above in a pharmaceutically acceptable excipient. The compositions are most preferably in the form of topical ophthalmic formulations for delivery to the eye. The compounds of the invention may be combined with ophthalmologically acceptable

preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution to form the compositions of the invention.

The compositions of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds of the invention as

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